PSJ3
Exhibit 168

To: Will Rowe[wrowe@painfoundation.org]
From: Rosen, Burt
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To FDA

The undersigned write to urge the Food and Drug Administration to adopt a class-wide Risk Evaluation and Mitigation Strategy ("REMS") for opioid analgesics. The possibility of a class REMS was discussed during the November 13 and 14, 2008 Advisory Committee meetings regarding the pending applications for two investigational pain medications. During those meetings, concern was expressed by a number of public participants about the potential for multiple, overlapping REMS programs to overwhelm physicians and pharmacists and to interfere with patient care. Dr. Rappaport indicated that FDA preferred a class approach and that the Agency is actively discussing use of its new REMS authority in order to develop a class REMS for opioid analgesics.

A Class-Wide REMS is Essential

The undersigned believe it is essential that REMS requirements for opioid analgesics be developed and implemented on a consistent and class-wide basis. As discussed during both the recent Advisory Committee hearing and the June 2007 public workshop on Risk Minimization Action Plans (RiskMAPs), the proliferation of product-specific REMS (and their predecessor RiskMAPs), has burdened physicians, pharmacists, and patients. Inconsistencies and differences between programs with similar elements have been particularly troublesome. In the case of opioid analgesics, the risks to be managed – e.g., proper patient selection and dosing (including evidence of opioid tolerance prior to using higher strength dosage units), the risk of opioid misuse, abuse and diversion, safe storage and disposal, the management of side-effects, the potential for accidental or intentional overdose, how to discontinue an opioid analgesic – are similar. Therefore a class approach is not only feasible, but the most efficient means of addressing these risks without unduly impeding patient access to these essential medicines. Moreover, because of the widespread use of products in this class, and the correspondingly large number of specialists and general practitioners prescribing these products (estimated at [insert number if available]), a patchwork of product-specific REMS is not practical or feasible.

Moreover, imposition of restricted distribution requirements on one drug or group of drugs can be expected to systematically increase prescriptions for other similar drugs that are not subject to the same burdensome and time consuming requirements. Thus, piecemeal application of product-specific REMS for opioid analgesics may simply shift, without actually mitigating, the various risks associated with this class, while simultaneously denying some patients access to the medicine their prescriber recommends. For example, as noted in the FDA briefing materials for the Advisory Committee hearing on November 14, 2008, historically, when availability of one drug with abuse potential has been curtailed, abuse of another similar drug generally increases. In addition to the impact on nonmedical use, uneven application of restricted

distribution requirements among opioid analgesics would likely mean that patients do not receive the drug most suitable to treat their condition, either because the available doctor or pharmacy is not enrolled in the relevant REMS program, or because the patient requires therapy immediately and cannot wait for completion of a lengthy registration process.

For all of these reasons, we strongly support development and implementation of a class-wide REMS for opioid analgesics.

Elements of a Class-Wide REMS

In developing a class REMS for opioid analgesics, it is critical that the Agency appreciate that, just as a host of product-specific REMS requirements would cripple already overburdened healthcare practitioners and pharmacists, so too would a poorly designed class REMS. Indeed, in 2002, the Agency held an Advisory Committee meeting to discuss the use of opioid analgesics in pain patients, as well as their potential for abuse and misuse. At that meeting it was concluded that, while abuse of opioids is a significant public health problem, these drugs are important for proper pain management and an overly restrictive risk management plan may limit the proper use of these drugs in patients with legitimate medical need. FDA echoed these concerns during the May 6, 2008, Advisory Committee meeting concerning Fentora, acknowledging that some prescribers and/or pharmacies may choose not to participate in burdensome REMS programs, disrupting and even preventing patent access.

In light of these significant concerns, FDA must consult not only with the affected sponsors, but also with other stakeholders who will be impacted by REMS requirements for opioid analgesics, including prescribers, pharmacists, wholesalers, and patients and those who advocate for appropriate pain care. Previous approaches to risk minimization, in this category and others, must be carefully evaluated to ensure that only those elements likely to mitigate the relevant risks are implemented, and that elements are implemented in the least burdensome manner possible.

In considering the appropriate elements to include in a class REMS for opioid analgesics, we encourage FDA to implement targeted physician and pharmacist education and certification requirements as a prerequisite to prescribing and dispensing these products. Extreme care must be taken in designing such a program, however, to ensure such requirements are not so logistically burdensome as to discourage or prevent prescriber and pharmacist participation. While some previous REMS have employed education and certification requirements seemingly without impeding access to the subject medication, as alluded to above, a class REMS for opioid analgesics would impact a far larger number of healthcare professionals treating a far larger number of patients. These patients suffer from a variety of underlying conditions

causing pain and warranting treatment with opioid analgesics, and obtain their prescriptions from a variety of specialists as well as general practitioners. These differences necessitate different approaches to education and certification requirements than have historically been employed. To ensure continued access by all patients, including those living in underserved areas of the country, such requirements must be carefully designed, with the goal of properly educating and certifying all existing prescribers and dispensing pharmacies, as well as any new prescribers and pharmacies interested in participating. Finally, the requirements must be phased in slowly, over time, so that physicians and pharmacists may continue to prescribe and dispense while preparing to fulfill the new requirements.

The undersigned do not believe that a class REMS for opioid analgesics should include a patient registry. Such registries raise serious patient privacy concerns and could prove to be a significant barrier to proper patient care. Moreover, if patient information collected in the course of patient registration and tracking is properly maintained as confidential in order to address these privacy concerns, then it is not clear that requiring patient registration and collecting the related patient information would be of any benefit in addressing the risks the REMS is attempting to mitigate.

In addition to concerns about patient privacy, a patient registry also poses logistical concerns. Given the large number of patients taking opioid analgesics, and the wide range of branded and generic opioid analgesic products, a comprehensive registry is not feasible. Enrolling patients in such registries, and confirming proper enrollment at the pharmacy, is extraordinarily time consuming. While many physicians and pharmacists have thus far managed these burdens in individual RiskMAP programs, others have declined to participate in programs that include requirements for patient registries. Any attempt to register the large number of patients treated with opioid analgesics would paralyze existing systems. Recognizing the magnitude of the time commitment, many prescribers and pharmacists will opt not to participate, resulting in significant barriers to access. Even among those willing to participate, people in need of opioid analgesics generally cannot, and should not have to, wait for them while a lengthy registration process is completed.

Authority to Develop a Class-Wide REMS

The new FDAAA REMS provisions specifically provide FDA with the authority to consider and address class-wide risks via REMS. 21 U.S.C. § 355-1(h)(7). These provisions contemplate that in cases of serious risks related to a pharmacological class, FDA will meet with the affected sponsors, stakeholders, and Advisory Committees to develop a regulatory plan to address the class-wide risks. We believe these procedures are well suited to developing a class REMS for opioid analgesics.

[Insert conclusion and signatures]

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Sources for Some of the Above:

Background: At the 5/08 OTR Advisory Committee Hearing, Mwango Kashoki, MD, MPH, Medical Team Leader, Division of Anesthesia, Analgesia, and Rheumatology Products gave a presentation "History of OxyContin: Labeling and Risk Management Program" in which she stated, "Later in 2002, the Agency held an Advisory Committee meeting to discuss the use of opioid analgesics in pain patients, as well as their potential for abuse and misuse. And at this meeting, it was concluded that while abuse of opioids is a significant Public Health problem, these drugs are important for proper pain management. And an overly restrictive risk management plan may limit the proper use of these drugs in legitimate patients."

Background: Jeanine Best, Senior Drug Risk Management Analyst, Division of Risk Management, Office of Surveillance and Epidemiology – speaking at the May 6th Advisory Committee Hearing re: Fentora – stated "Additional risk mitigation strategies may be more burdensome depending on the requirements imposed. And because of the increased burden, some prescribers and/or pharmacies may choose not to participate. This can have an unintended consequence in that appropriate patients could have delayed or no access to the product"

In June 2007, the Agency for Healthcare Research and Quality (AHRQ) and FDA jointly conducted a 2-day public workshop entitled "Implementation of Risk Minimization Action Plans (RiskMAPs) to Support Quality Use of Pharmaceuticals: Opportunities and Challenges." The workshop focused on RiskMAPS with restricted distribution systems and sought input from various stakeholders, including clinicians, pharmacists, patients, third party payers, and industry. At the workshop, a number of organizations explained the significant difficulties restricted distribution systems present for pharmacists. Groups called for the standardization of programs to the extent possible, and the use of restricted distribution systems only for a limited number of products, where no other means of controlling risk was available. Speakers also discussed the administrative burden on physicians. Some physicians are reluctant to enroll in these programs and some enrolled physicians do not prescribe. There are implications for patient access.